REMARKS

Upon entry of the above amendment, claims 86-94 will be pending in this application. The claim amendments do not introduce any new matter.

1. Consideration of IDS references

Applicants note the Examiner's statement on page 2 of the Official Action that "[d]ocuments with no year of publication provided were not considered." In this regard, applicants note that the Examiner did not consider one reference filed in October 2005 to Kato et al.

Applicants respectfully submit that this reference was published April 28, 2001. Further, applicants respectfully request consideration of this reference and request that the Examiner send applicants proof that this reference has been properly considered such as a signed 1449 form.

2. Rejection of claims under 35 U.S.C. §103(a)

The Official Action states that claims 39, 41-46, 75, 77 and 84 are rejected under 35 U.S.C. §103(a) as being unpatentable over the disclosure contained in Sigmund et al., Reid and Sacchi et al.

RESPONSE

First, Applicants respectfully note that the rejected claims have been canceled without prejudice to or disclaimer of the subject matter contained therein, rendering the

basis for this rejection moot.

With regards to a similar rejection being made over presently pending claims 86-94, Applicants respectfully traverse this rejection. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

To establish a prima facie case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in KSR International Co. v. Teleflex Inc. et al., Slip Opinion No. 04-1350, 550 U.S. _____(April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (KSR, supra, slip opinion at 13-15). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Amgen Inc. v. Chugai Pharm. Co., 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or

suggest all the limitations of the claims. In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

The Sigmund et al. publication describes that selective PDE4 inhibitors seem to have an effect in B cell chronic lymphocytic leukemia (B-CLL). In this regard, the Abstract states that "Rolipram, a specific inhibitor of PDE4, the predominantly expressed in B-CLL cells, has been shown to induce cAMP dependent apoptosis in these cells. [...] In conclusion, by inducing apoptosis, by enhancing apoptosis induced by fludarabine, by suppressing Bcl-2, Bcl-X and by inducing Bax expression, PDE4 inhibitors may add a new therapeutic option for patients with B-CLL."

It is respectfully submitted that the combination of fludarabine plus rolipram increased apoptosis as compared to the administration of rolipram or fludarabine alone. However, the effect was neither additive nor synergistic. Further, the combination of rolipram and mitoxantrone did not significantly increase apoptosis compared to mitoxantrone alone. Thus, there is no teaching whatsoever contained in the Sigmund et al. reference that rolipram or PDE4 inhibitors in general might also be useful in the treatment of the disease acute myeloid leukemia (AML) which is different from chronic lymphocytic leukemia (CLL).

AML and CLL are different disease entities based on the fact that AMP is about a differentiation block in granulocyte precursors preventing formation of differentiated granulocytes and promoting excessive (neoplastic) proliferation of immature myeloid precursor cells. In CLL, there is (neoplastic) accumulation of lymphocyctes in particular of mature B-cells that escaped apoptosis. Different disease mechanisms are behind

these ailments. Thus, the Examiner should not automatically conclude that therapeutic concepts acting in CLL are of benefit in AML and vice versa.

The secondary Reid and Sacchi et al. references do not remedy the deficiencies of the primary Sigmund et al. reference in establishing a *prima facie* case of obviousness against the presently pending claims. Neither the Reid nor the Sacchi et al. references fairly teach the specific methods of treating AML, nor the specific treatment combinations as presently claimed.

As such, the combination of the Sigmund et al., Reid and Sacchi et al. references fail to establish a *prima facie* case of obviousness against the presently pending claims because the cited references fail to teach each and every element of the presently pending claims as required by In re Wilson.

Accordingly, the Examiner is respectfully requested to withdraw this rejection of presently pending claims.

3. Rejection of claims under 35 U.S.C. §103(a)

The Official Action states that claims 39, 41-46, 75, 77 and 84 are rejected under 35 U.S.C. §103(a) as being unpatentable over the disclosure contained in Sigmund et al., Reid, Sacchi et al., as outlined above, and further in view of Lerner and Keeping.

RESPONSE

As outlined above, Applicants respectfully note that the rejected claims have been canceled without prejudice to or disclaimer of the subject matter contained therein, rendering the basis for this rejection moot.

With regards to a similar rejection being made over presently pending claims 86-94, Applicants respectfully traverse this rejection. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

For the sake of brevity, applicants incorporate by reference in their entirety, the arguments presented above regarding the teachings of the Sigmund, Reid and Sacchi et al. references. Applicants will now discuss the deficient teachings contained in the Lerner et al and Keeping references.

The Lerner et al. reference does not go beyond the teachings contained in the Sigmund et al. reference. In particular, the Abstract states, in relevant part: "...inhibition of PDE4 results in uniquely potent induction of apoptosis in CLL cells. [...] Clinical trials utilizing PDE4 inhibitors are indicated in the therapy of CLL patients resistant to standard therapy." Further, on page 47, right column, Lerner et al. state "...inhibitors of PDE4 consistently induce apoptosis in CLL cells. The ability of a given concentration of PDE4 inhibitor to induce apoptosis in CLL cells correlates tightly with its ability to raise cAMP levels in these cells." As with the Sigmund et al. reference, there is no teaching whatsoever by Lerner et al. that rolipram or PDE4 inhibitors in general might also be useful in the treatment of the disease acute myeloid leukemia (AML).

Further, the Keeping reference is not relevant to the presently pending claims because it contains teachings only related to compounds that raise intracellular concentrations of cAMP. The presently pending claims are not directed to such subject matter. As such, Keeping does not contain any disclosure that remedies the deficient teachings of the above cited references.

As such, the combination of the Sigmund et al., Reid, Sacchi et al., Lerner et al. and Keeping references fail to establish a *prima facie* case of obviousness against the presently pending claims because the cited references fail to teach each and every element of the presently pending claims as required by In re Wilson.

Accordingly, the Examiner is respectfully requested to withdraw this rejection of presently pending claims.

CONCLUSION

Based upon the remarks, the presently claimed subject matter is believed to be patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 86-94. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments. The Examiner is specifically authorized to charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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APPENDIX A

Claim Amendments

1.-85. (Canceled)

86. (New) A method of treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof.

87. (New) The method according to claim 86, wherein the compound is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable salt thereof.

88. (New) The method according to claim 86, wherein the compound is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) or a pharmaceutically acceptable salt thereof.

89. (New) A method for treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal therapeutically effective amounts of

(i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and

(ii) all trans retinoic acid.

90. (New) The method according to claim 89, wherein the compound is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable salt thereof.

91. (New) The method according to claim 89, wherein the compound is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) or a pharmaceutically acceptable salt thereof.

92. (New) A treatment combination for acute myeloid leukemia (AML) comprising

(i) a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and

(ii) all trans retinoic acid.

93. (New) The treatment combination according to claim 92, wherein the compound of component (i) is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] or a pharmaceutically acceptable salt thereof.

94. (New) The treatment combination according to claim 92, wherein the compound of component (i) is 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) or a pharmaceutically acceptable salt thereof.